(54) Title: SENSOR ARRAYS FOR RESOLUTION OF ENANTIOMERS

(57) Abstract

The present invention relates to an array of sensors useful for constructing "electronic noses" for analyzing chiral analytes and producing a sample output. The array comprises compositionally different sensors, wherein a sensor comprises a chiral region. The analyte generates a differential electrical response across the sensor thereby being detected.

SENSOR ARRAYS FOR RESOLUTION OF ENANTIOMERS

CROSS-REFERENCE OF RELATED APPLICATIONS

This application claims priority to U.S. Application Serial Numbers 60/073,896, filed February 6, 1998 and 60/074,094, filed February 9, 1998, the disclosures of which are incorporated herein by reference in their entirety for all purposes.

FIELD OF INVENTION

This invention relates generally to electrical sensors for detecting analytes in fluids. More particularly, it relates to an array of sensors useful for constructing "electronic noses" for analyzing chiral analytes and differentiating between optical isomers.

BACKGROUND OF THE INVENTION

In sensor arrays that use broadly cross-reactive detectors, no individual detector responds solely to a specific molecule, but the collective response of the entire array of detectors yields a unique fingerprint for the analyte of interest (*see*, U.S. Patent Nos. 5,571,401, 5,698,089, 5,788,833 and Lonergan, M.C. *et al., Chem. Mater.* 1996, 8, 2298). Such arrays are often referred to as "electronic noses" and are developed to classify, identify, and quantify vapors based on pattern recognition algorithms (*see*, Zaromb, S. *et al., Sens. Actuators* 1984, 6, 225; Lundstrom, I. *et al., Nature* 1991, 352, 47; Shurmer, H.V. *et al., Sens. Actuators* B 1992, 8, 1; Gardner, J.W. *Sens. Actuators* B 1994, IB, 211; Gardner, J.W. *et al., Sens. Actuators* 13 1992, 9, 9; Nakamoto, T. *et al., Sens. Actuators B* 1993, 10, 85.). In this approach, the detection takes advantage of the collective output of an array of broadly responsive detectors.

In general, electronic noses are artificial sensory systems that are able to mimic chemical sensing. For example, in a polymer composite array configuration that consists of insulator/conductor polymer composites, the signal transduction is straightforward: swelling of the polymeric phase of the composite in the presence of a

vapor, leads to an increase in the electrical resistance of the composite, which is monitored using simple electronics. Using these sensors, it is possible to detect volatile materials by directly or indirectly measuring the resistance across each of the sensors in the array. Moreover, by providing different variables in each sensor of the array, such as

5   the polymeric make-up of the sensors, it is possible to characterize various chemical materials according to the response of the array to the analyte of interest.

An ideal sensor array would produce a unique signature for every molecule to which it was exposed. In such a system, it would be necessary to include detectors that probe important, but possibly subtle, molecular parameters such as

10   chirality. Moreover, chirality is an important chemical phenomenon. Harnessing enantiomer resolution gives rise to myriad applications. For instance, because the active sites of enzymes are chiral, only the correct enantiomer is recognized as a substrate. Thus, pharmaceuticals having near enantiomeric purity are often many more times active than their racemic mixture. However, many pharmaceutical formulations marketed today

15   are racemic mixtures of the desired compound and its "mirror image." One optical form (or enantiomer) of a racemic mixture may be medicinally useful, while the other optical form may be inert or even harmful, as has been reported to be the case for thalidomide. Various methods exist which generate the correct enantiomer, including chiral synthesis, enzymatic resolution or some other means of obtaining the optically active compound.

20   Due to the wide range of industrial applications, there is a growing interest in finding ways to resolve racemic mixtures into optically active isomers, or to synthesize enantiomerically pure compounds directly and rapidly monitor the efficiency of such processes.

European Application No. 0 794 428 describes sensors capable of

25   distinguishing between enantiomers. The sensors comprise a pair of spaced apart contacts and a polymer material spanning the gap. The polymeric material is grown between the gaps; thus only a limited number of polymers can be used. This architecture limits the usefulness of these sensors because of their inherit low sensitivity.

As such, what is needed in the art is a sensor able to distinguish between

30   chiral molecules. Such sensor arrays would make it possible to achieve enantiomeric identification for a broad range of analytes. In addition, what is needed in the art are sensor arrays having additional detector elements that would be part of a larger detector

array system, thereby broadening the discrimination ability of such arrays towards chiral analytes. The present invention fulfills these and other needs.

SUMMARY OF THE INVENTION

5   In one aspect, the present invention relates to a device for detecting the presence or absence of an analyte in a fluid, the device comprises a sensor, the sensor comprising a chiral region. Preferably, the sensor comprises a conductive region and a nonconductive region, wherein at least one of the conductive and nonconductive regions is chiral, and wherein the analyte generates a differential response across the sensor. The

10   conductive region can be chiral, the nonconductive region can be chiral or both the conductive and nonconductive regions can be chiral. Preferably, the device comprises an array of sensors *i.e.*, two or more sensors comprising at least one sensor having a chiral region. Examples of differential responses that can be detected include, but are not limited to, electrical responses, such as resistance, impedance or capacitance, optical,

15   magnetic, surface acoustic and fluorescence responses. In a preferred embodiment, the chiral region comprises a chiral resolving agent, such as a chiral polymer.

A broad range of analytes can be detected using the sensors of the present invention. Detectable analytes include chiral analytes as well as analytes that are achiral. Suitable analytes include, but are not limited to, alkanes, alkenes, alkynes, dienes,

20   alicyclic hydrocarbons, arenes, alcohols, ethers, ketones, aldehydes, carbonyls, carbanions, heterocycles, polynuclear aromatics, organic derivatives, biomolecules, microorganisms, bacteria, viruses, sugars, nucleic acids, isoprenes, isoprenoids, fatty acids and their derivatives. Due to the presence of chiral moieties, many biomolecules, such as amino acids, are amenable to detection using the sensor arrays of the present

25   invention.

In another aspect, the present invention relates to a method for detecting an analyte in a fluid, the method comprising: contacting a device with an analyte, the device comprising a sensor, the sensor comprising a chiral region. Preferrably, the sensor comprises a conductive region and a nonconductive region, wherein at least one of the

30   conducting and nonconducting regions is chiral, and wherein the analyte generates a differential response across the sensor array; and measuring the response from a detector connected to the sensor, thereby detecting the presence or absence of the analyte. Preferably, the device comprises an array of sensors *i.e.*, two or more sensors.

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These and other features and advantages of the present invention will be more readily apparent and understood when read with the detailed description that follows.

5   **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 illustrates a typical response of a chiral detector to 2-butanol.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS ·

10   In certain aspects, the sensor or sensor arrays of the present invention are capable of distinguishing or differentiating between chiral compounds, such as enantiomers, *i.e.*, optical isomers. As such, the present invention relates to a device for detecting the presence or absence of an analyte in a fluid, the device comprises a sensor, the sensor comprising a chiral region. Preferably, the sensor comprises a conductive

15   region and a nonconductive region, wherein at least one of the conductive and nonconductive regions is chiral, and wherein the analyte generates a differential response across the sensor. In certain preferred embodiments, the analyte contacts the chiral region of the sensor. The analytes can be chiral or achiral. The term "chiral" is used herein to refer to an optically active or enantiomerically pure compound, or to a compound

20   containing one or more asymmetric centers in a well-defined optically active configuration. A chiral compound is not superimposable upon its mirror image. As used herein the term "optically active compound" refers to a compound having the ability to rotate the plane of polarized light.

Preferably, the devices of the present invention comprise at least two

25   sensors, *i.e.*, an array of sensors, wherein at least one sensor comprises a conductive region and a nonconductive region, wherein at least one of the conductive and nonconductive regions is chiral. The sensor arrays of the present invention comprise at least two different sensors. Preferably, each sensor comprises a first and second chemical lead in electrical communication to an analyte sensitive resistor. The leads are a

30   conductive material, such as a metal. The electrical leads are optionally interdigitized to maximize the signal-to-noise ratio.

Preferably, the sensor comprises regions of conductive material and regions of nonconductive material. The conductive region can be chiral, the

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nonconductive region can be chiral or both the conductive region and the nonconductive region can be chiral.   The array of sensors can comprise any combination of chiral region sensors.

In certain embodiments, the sensor comprises a plurality of interchanging nonconductive and conductive regions transverse to the electrical path between the conductive leads. The sensor can be fabricated by blending a conductive material with a nonconductive material, such as an organic polymer, in order that the electrically conductive path between the leads coupled to the sensor is interrupted by gaps of non-conductive regions. For example, in a colloid, suspension or dispersion of particulate conductive material in a matrix of nonconductive organic material, the matrix regions separating the particles provide the gaps. The nonconductive or insulating gaps range in path length from about 10 to 1,000 angstroms, usually on the order of 100 angstroms providing individual resistance of about 10 to 1,000 mΩ, usually on the order of 100 mΩ, across each gap.

In some instances, the conductive region of the sensor is a particulate material, such as carbon black, and the nonconductive region is an organic matrix, such as an organic polymer that separates the particulate material, thereby providing the gaps in the electrical path. In a preferred embodiment, the chiral region comprises a chiral material, such as an organic chiral resolving agent. An example of a chiral resolving agent is a chiral polymer.   Without being bound by any particular theory, it is believed that the path length and resistance of a given gap is not constant but rather changes as the nonconductive region absorbs, adsorbs or imbibes an analyte. Accordingly the dynamic aggregate resistance provided by these gaps in a given resistor is a function of analyte permeation of the nonconductive regions. The conductive region can also contribute to the dynamic aggregate resistance as a function of analyte permeation (*e.g.*, when the conductive material is a conductive organic polymer such as polypyrrole.)

Chemical sensitivity varies across the sensor array by qualitatively or quantitatively varying the composition of the conductive and/or nonconductive regions. For instance, the conductive material can be different in each sensor. Alternatively, the concentration of the chiral resolving agent can be varied, or the chiral resolving agent itself can be varied and changed. Using qualitative or quantitative variations in sensor design and architecture, an array of sensors can be constructed.   In some instances, the sensor array of the present invention comprises about 2 to about 100 sensors. In other

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embodiments, the sensor array comprises about 100 to about 1000 sensors. In still other

embodiments, the array comprises about 1000 to about 10^6 sensors.

    The sensor or array of sensors of the present invention comprise a chiral

region. In certain instances, the sensor comprises a conductive region, a nonconductive

5   region or both a conductive region and a nonconductive region. Various sensors suitable

for chiral detection using the present invention include, but are not limited to, thermal

sensors, radiation sensors, mechanical sensors, magnetic sensors, chemical sensors,

biological sensors and electrical sensors. The foregoing sensors have been classified by

their principal form of signal.

10   Measuring parameters for thermal sensors include, but are not limited to,

temperature, heat, heat flow, entropy, heat capacity *etc*. Measuring parameters for

radiation sensors include, but are not limited to, gamma rays, X-rays, ultra-violet rays,

visible, infrared, microwaves and radio waves. Measuring parameters for mechanical

sensors include, but are not limited to, displacement, velocity, acceleration, force, torque,

15   pressure, mass, flow, acoustic wavelength, and amplitude. Measuring parameters for

magnetic sensors include, but are not limited to, magnetic field, flux, magnetic moment,

magnetization, and magnetic permeability. Measuring parameters for chemical sensors

include, but are not limited to, humidity, pH level, concentration of analyte, vapor, odor,

toxic and flammable materials. Measuring parameters for biological sensors include, but

20   are not limited to, biomolecules such as sugars, proteins, haptens and antibodies.

Measuring parameters for electrical sensors include, but are not limited to, charge,

current, voltage, resistance, conductance, capacitance, inductance, dielectric permittivity,

polarization and frequency.

    In certain embodiments, thermal sensors are suitable for use in the present

25   invention that include, but are not limited to, thermocouples, such as a semiconducting

thermocouples, noise thermometry, thermoswitches, thermistors, metal thermoresistors,

semiconducting thermoresistors, thermodiodes, thermotransistors, calorimeters,

thermometers, indicators, fiber optics and surface acoustic wave sensors.

    In other embodiments, various radiation sensors are suitable for use in the

30   present invention that include, but are not limited to, nuclear radiation microsensors, such

as scintillation counters and solid state detectors, ultra-violet, visible and near infrared

radiation microsensors, such as photoconductive cells, photodiodes, phototransistors,

infrared radiation microsensors, such as photoconductive IR sensors and pyroelectric sensors.

In certain other embodiments, various mechanical sensors are suitable for use in the present invention that include, but are not limited to, displacement microsensors, capacitive and inductive displacement sensors, optical displacement sensors, ultrasonic displacement sensors, pyroelectric, velocity and flow microsensors, transistor flow microsensors, acceleration microsensors, piezoresistive microaccelerometers, force, pressure and strain microsensors, surface acoustic wave resonant devices and piezoelectric crystal sensors.

In yet still further embodiments, various magnetic sensors are suitable for use in the present invention that include, but are not limited to, Hall devices, magnetoresistors magnetodiodes, magnetotransistors, carrier domain MOS devices, SAW devices and superconducting quantum interference devices.

In certain other embodiments, various chemical or biochemical sensors are suitable for use in the present invention that include, but are not limited to, metal oxide gas sensors, such as tin oxide gas sensors, organic gas sensors, chemocapacitors, chemoidiodes, such as inorganic Schottky device, metal oxide field effect transistor (MOSFET), piezoelectric devices, ion selective FET for pH sensors, polymeric humidity sensors, electrochemical cell sensors, pellistors gas sensors, piezoelectric or surface acoustical wave sensors, infrared sensors, surface plasmon sensors, and fiber optical sensors.

Various other sensors suitable for use in the present invention include, but are not limited to, sintered metal oxide sensors, phthalocyanine sensors, membranes, Pd-gate MOSFET, electrochemical cells, conducting polymer sensors, lipid coating sensors and metal FET structures. In certain preferred embodiments, the sensors include, but are not limited to, metal oxide sensors such as a Tuguchi gas sensors, catalytic gas sensors, organic semiconducting gas sensors, solid electrolyte gas sensors, piezoelectric quartz crystal sensors, fiber optic probes and Langmuir-Blodgett films.

In certain embodiments, the chiral region of the sensors of the present invention comprises a chiral resolving agent. The chiral region can be a conductive region, a nonconductive region or both a conductive region and the nonconductive region. Suitable chiral resolving agents include, but are not limited to, chiral molecules, such as chiral polymers; natural products, such as, tartaric, malic and mandelic acids; alkaloids,

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such as brucine, strychnine, morphine and quinine; lanthanide shift reagents; chelating
agents; biomolecules, such as proteins, cellulose and enzymes; and chiral crown ethers
together with cyclodextrins. (*see*, E. Gassmann *et al.*, "Electrokinetic Separation of Chiral
Compounds," *Science*, vol. 230, pp. 813-814 (1985); and R. Kuhn et al., "Chiral

5   Separation by Capillary Electrophoresis," *Chromatographia*, vol. 34, pp. 505-512
(1992)). Additional chiral resolving agents suitable for use in the present invention will
be known by those of skill in the art.

In certain embodiments, the chiral resolving agent is a chiral polymer.
Chiral polymers suitable for use in the present invention include, but are not limited to,

10   homopolymers, heteropolymers and copolymers. Suitable chiral polymers contain at least
one optical center making them chiral polymers, *i.e.*, the polymers contain at least one
asymetric center in a monomeric moiety. In most instances, the monomeric chiral moiety
will be a plurality of chiral monomeric units. In certain embodiments, the chiral polymer
will have about 1 % to about 100 % enantiomeric purity. In other embodiments, the

15   chiral polymer will have about 10% to about 50 % enantiomeric purity or, more
preferably, about 50 % to about 90 % enantiomeric purity.

In some instance, the chiral or optical center can be part of a homopolymer
or, alternatively, the chiral or optical center can be introduced into a polymer structure by
way of copolymerizing an achiral monomer with a chiral monomer. Suitable chiral

20   monomers include, but are not limited to, R or S-methyl bezylacryamide, or other suitable
acrylamide derived from the reaction between acryloyl chloride and a suitable R or S-
primary or secondary amine and the like, and combinations thereof (*see*, U.S. Patent No.
5,739,383, which issued to Yoon *et al.*, on April 14, 1998). In another embodiment,
chiral arylcarboxamide-containing alkenes and alkoxysilanes and polysiloxanes polymers

25   containing chiral arylcarboxamide-substituted side chains are suitable for use in the
present invention. The foregoing chiral polymers are disclosed in U.S. Patent No.
4,909,935, which issued to Bradshaw *et al.*, on March 20, 1990.

A chiral center can be incorporated into a polymer using various
techniques. For instance, the chiral moiety can be included as a side chain, or as a

30   counter ion, or the polymer can be synthesized in a chiral solvent. In one illustrative
embodiment, the chiral polymer is a copolymer, such as poly(R-3-hydroxybutyrate-
co-R-3-hydroxy-valerate), having about 77% butyrate. This polymer is commercially
available from Goodfellow Corporation (Berwyn, PA).

Polymer particles having a hydrophobic core and various surface functional groups, particularly, chiral functional groups such as described in U.S. Patent No. 5,306,561, which issued to Frechet *et al.*, can also be used. The functional monomers that result in chiral surface functionality are those monomers that contain a

5 polymerizable vinyl group and a reactive chiral group. Suitable reactive chiral groups include, but are not limited to, amino acids, alcohols, amines, esters, amides, sugars, carboxylic acids, esters, and the like. Accordingly, suitable monomers can be produced by the attachment of known optically active (chiral) compounds to styrenic, acrylic, methacrylic or other vinylic structure that can be polymerized by conventional free-

10 radical techniques. Generally, the attachment will result in pendant chiral groups such as those listed above.

In other embodiments, the chiral resolving agent is mixed or incorporated into an organic matrix. Such an organic matrix can be an organic polymer that optionally contains a chiral solvent, or a chelating agent. Organic polymers suitable for use in the

15 present invention include, but are not limited to, those set forth in U. S. Patent No. 5,571,401, which issued to Lewis *et al.*

In another embodiment, the chiral region is formed using template polymerization, wherein the chiral analyte molecule serves as a template to assemble its own recognition sites in a polymer (*see*, U.S. Patent No. 5,786,428, which issued to

20 Arnold, *et al.*). In this aspect, the chiral region comprises a polymer matrix that contains one or more metal complexes that are oriented within the polymer matrix to provide selective binding of the matrix to one enantiomer of an optically active compound. The metal complexes responsible for binding the analyte includes a polymerizable moiety that allows the complex to be copolymerized with monomers and crosslinking agents to form

25 molecularly imprinted porous polymeric material. The metal complexes must be able to form rapidly reversible mixed-ligand complexes with the analyte molecule. Exemplary functional groups that can be attached to the metal complex to form polymerizable metal complexes include, but are not limited to, styrene, methacrylate, acrylate, vinyl, vinyl ether, vinyl acetate, trialkoxysilane, dialkylchlorosilane and epoxy.

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In another embodiment, the polymer that serves as the chiral region incorporates chiral counter ions as discussed in EP 0 794 428. In this embodiment, the optically active counter ion includes a sulfonic acid moiety. Suitable optically active side chains include, but are not limited to, menthoxy acetic acid, carzyl acetate and natural or synthetic chiral amino acids. A semi-conducting polymer material comprising the chiral counter ions spans the gap between electrical contacts, wherein the polymer material is such that its electrical resistance changes on exposure to volatile enantiomeric substances.

In still further embodiments, the chiral region is a polymerized chiral micelle. Such chiral micelles are disclosed in U.S. Patent No. 5,770,084. Suitable chiral micelles include, but are not limited to, poly(sodium N-undecylenyl-L-valinate) and poly (sodium N-undecylenyl-D-valinate) and combinations thereof.

A wide variety of conductive materials that make up the conductive region can be used in the sensor arrays of the present invention. In some instances, the conductive region is chiral. Table 1 sets forth exemplary conductive materials for use in resistor fabrication. Mixtures of conductive materials, such as those listed, can also be used.

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Table 1

Major Class	Examples
Organic Conductors	conducting polymers (poly(anilines), poly(thiophenes), poly(pyrroles), poly(acetylenes), *etc.*)), carbonaceous materials (carbon blacks, graphite, coke, C_{60}, *etc.*), charge transfer complexes (tetramethylparaphenylenediamine-chloranile, alkali metal tetracyanoquinodimethane complexes, tetrathiofulvalene halide complexes, etc.), *etc.*
Inorganic Conductors	metals and metal alloys (Ag, Au, Cu, Pt, AuCu alloy, *etc.*), highly doped semiconductors (Si, GaAs, InP, MoS_2, TiO_2, *etc.*), conductive metal oxides (In_2O_3, SnO_2, $Na_xPt_3O_4$, *etc.*), superconductors ($YBa_2Cu_3O_7$, $Tl_2Ba_2Ca_2Cu_3O_{10}$, *etc.*), *etc.*
Mixed inorganic/organic Conductors	Tetracyanoplatinate complexes, Iridium halocarbonyl complexes, stacked macrocyclic complexes, *etc.*

In still yet another embodiment, the conductive region can be a conductive

5   particle, such as a colloidal nanoparticle. As used herein the term "nanoparticle" refers to

a conductive cluster, such as a metal cluster, having a diameter on the nanometer scale.

Examples of colloidal nanoparticles for use in accordance with the present invention are

described in the literature (*see*, Templeton *et al. J. Am. Chem. Soc.* (1998) **120**

:1906-1911; Lee *et al., Isr. J. Chem.* (1997) **37**: 213-223 (1997); Hostetler *et al.*

10   *LANGMUIR* (1998) **14**:17-30; Ingram *et al., J. Am. Chem. Soc.*, (1997) **119** :9175-9178;

Hostetler *et al., J. Am Chem. Soc.*(1996) **118** :4212-4213; Henglein *J. Phys. Chem.*

(1993) 97 :5457-5471; Zeiri, *J. Phys. Chem.*(1992) 96 :5908-5917; Leff *et al.*, *LANGMUIR* (1996) 4723-4730. In this embodiment, the nonconductive region can optionally be a ligand comprising a chiral moiety that is attached to a central core making up the nanoparticle. These ligands *i.e.*, caps, can be polyhomo or

5   polyheterofunctionalized, thereby being suitable for detecting a variety of chemical analytes.

In certain embodiments, the resistors are nanoparticles comprising a central core conducting element and an insulating attached ligand optionally in a polymer matrix. With reference to Table 1, various conducting materials are suitable for the

10   central core. In certain preferred embodiments, the nanoparticles have a metal core. Preferred metal cores include, but are not limited to, Au, Ag, Pt, Pd, Cu, Ni, AuCu and mixtures thereof. Gold (Au) is especially preferred. These metallic nanoparticles can be synthesized using a variety of methods. In a preferred method of synthesis, a modification of the protocol developed by Brust *et al.* can be used. (*see*, Brust, M.;

15   Walker, M.; Bethell, D.; Schiffrin, D.J.; Whyman, R. *J. Chem. Soc., Chem. Commun.*, **1994**, 801-802.)

Chiral ligands or caps of various chemical classes are suitable for use in the present invention. Ligands include, but are not limited to, alkanethiols having alkyl chain lengths of about C_1-C_{30}. Alkanethiols suitable for use can also be polyhomo-

20   functionalized or polyheterofunctionalized (such as, at the ω-position, or last position of the chain). As used herein, the term "polyhomofunctionalized" means that the same chemical moiety has been used to modify the ligand at various positions within the ligand. The ligands can be attached to the central core by various methods including, but not limited to, covalent attachment, and electrostatic attachment. As used herein, the term

25   "polyheterofunctionalized" means that different chemical moieties or functional groups are used to modify the ligands at various positions. In addition to alkanethiols, various suitable ligands include, but are not limited to, polymers, such as polyethylene glycol; surfactants, detergents, biomolecules, such as polysaccharides: protein complexes, polypeptides, dendrimeric materials, oligonucleotides, fluorescent moieties and

30   radioactive groups.

Nonconducting polymers suitable for use in the present invention include, but are not limited to, main-chain carbon polymers, such as poly(dienes), poly(alkenes), poly(acrylics), poly(methacrylics), poly(vinyl ethers), poly(vinyl thioethers), poly(vinyl

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alcohols), poly(vinyl ketones), poly(vinyl halides), poly(vinyl nitriles), poly(vinyl esters), poly(styrenes), poly(arylenes); main-chain acyclic heteroatom polymers, such as poly(oxides), poly(carbonates), poly(esters), poly(anhydrides), poly(urethanes), poly(sulfonates), poly(siloxanes), poly(sulfides), poly(thioesters), poly(sulfones),

5   poly(sulfonamides), poly(amides), poly(ureas), poly(phosphazenes), poly(silanes), poly(silazanes); and main-chain heterocyclic polymers, such as poly(furan tetracarboxylic acid diimides), poly(benzoxazoles), poly(oxadiazoles), poly(benzothiazino-phenothiazines), poly(benzothiazoles), poly(pyrazinoquinoxalines), poly(pyromellitimides), poly(quinoxalines), poly(benzimidazoles), poly(oxindoles),

10   poly(oxoisoindolines), poly(dioxoisoindolines), poly(triazines), poly(pyridazines), poly(piperazines), poly(pyridines), poly(piperidines), poly(triazoles), poly(pyrazoles), poly(pyrrolidines), poly(carboranes), poly(oxabicyclononanes), poly(dibenzofurans), poly(phthalides), poly(acetals), poly(anhydrides) and carbohydrates.

The sensors of the present invention can be fabricated using numerous

15   techniques including, but not limited to, solution casting, suspension casting and mechanical mixing. In general, solution casting routes are advantageous because they provide homogeneous structures and are easy to process. With solution casting routes, resistor elements can be easily fabricated by spin, spray or dip coating. Since all elements of the resistor must be soluble, solution casting routes can be somewhat limited in their

20   applicability. Suspension casting still provides the possibility of spin, spray or dip coating, but more heterogeneous structures than those formed with solution casting are expected. With mechanical mixing, there are no solubility restrictions since this technique involves only the physical mixing of the resistor components, but device fabrication is more difficult since spin, spray and dip coating are no longer possible. In

25   certain embodiments, the resistor is deposited as a surface layer on a solid matrix that provides means for supporting the leads. Typically, the solid matrix is a chemically inert, nonconductive substrate, such as a glass or ceramic.

Sensor arrays of the present invention are particularly well suited to scaled up production by being fabricated using integrated circuit (IC) design technologies. For

30   example, the chemiresistors can easily be integrated onto the front end of a simple amplifier interfaced to an A/D converter to efficiently feed the data stream directly into a neural network software or hardware analysis section. Micro-fabrication techniques can integrate the chemiresistors directly onto a microchip that contains the circuitry for analog

signal conditioning/processing and then data analysis. This provides for the production of millions of incrementally different sensor elements in a single manufacturing step using ink-jet technology. Controlled compositional gradients in the chemiresistor elements of a sensor array can be induced in a method analogous to how a color ink-jet printer deposits

5   and mixes multiple colors. However, in this case, rather than multiple colors, a plurality of different polymers in a solution that can be deposited are used. A sensor array of a million distinct elements only requires a 1 cm x 1 cm sized chip employing lithography at the 10 µm feature level, which is within the capacity of conventional commercial processing and deposition methods. This technology permits the production of sensitive,

10   small-sized, stand-alone chemical sensors.

Preferred sensor arrays have a predetermined inter-sensor variation in the structure or composition of the chiral region (e.g., the chiral conductive material, the chiral nonconductive material or both the conductive and nonconductive materials.) The variation can be quantitative and/or qualitative. For example, the concentration of chiral

15   material can be varied across sensors. Alternatively, the chiral resolving agent within the chiral region can be varied.

In another aspect, the present invention relates to a method for detecting an analyte in a fluid, the method comprising: contacting a device with said analyte, said device comprising a sensor, said sensor comprising a chiral region and wherein the

20   analyte generates a differential response across the sensor; and measuring the response from a detector connected to the sensor, thereby detecting the presence or absence of the analyte. Preferrably, the sensor comprising a conductive region and a nonconductive region wherein at least one of the conducting and nonconducting regions is chiral. Using this method, it is possible to differentiate between optical isomers or enantiomers.

25   Preferably, the device comprises an array of sensors.

An electronic nose for detecting an analyte, optionally a chiral analyte, in a fluid is fabricated by electrically coupling the sensor leads of an array of compositionally different sensors to a measuring device, such as an electrical measuring device. The sensor can measure changes in resistively, capacitance, impedance or other electrical

30   responses at each sensor of the array, or other responses such as optical, magnetic or fluorescence responses. Preferably the response is simultaneously measured over the array and preferably over a period of time. Frequently, the device includes signal

processing means and is used in conjunction with a computer and data structure for comparing a given response profile to a structure-response profile database for qualitative and quantitative analysis.

As such, in another embodiment, the present invention, relates to a system for detecting an analyte in a fluid, comprising: a device comprising a sensor, the sensor comprising a conductive region and a nonconductive region, wherein at least one of the conducting and nonconducting regions is chiral and wherein the analyte generates a differential response across the sensor; a measuring device connected to the sensor, and a computer comprising a resident algorithm; the measuring device measuring the response from the sensor, thereby detecting the presence or absence of the analyte and the computer assembling the responses into a sensor response profile. Preferably, the sensor is an array of sensors and the response is an electrical response.

In a preferred operation with an array of sensors, each sensor, such as a resistor, provides a first response, such as an electrical response, between its conductive leads when the sensor is contacted with a first fluid comprising an analyte at a first concentration, and a second response between its conductive leads when the sensor is contacted with a second fluid comprising the same analyte at a second different concentration. The fluids can be liquid or gaseous in nature. The first and second fluids may reflect samples from two different environments, a change in the concentration of an analyte in a fluid sampled at two time points, a sample and a negative control, *etc.* The sensor array necessarily comprises sensors that respond differently to a change in an analyte concentration, *i.e.*, the difference between the first and second response, such as an electrical resistance, of one sensor is different from the difference between the first and second response of another sensor. In addition, the sensor array can comprise redundant sensors that can be advantageous for maximizing the signal and thus reducing the noise in the signal.

In a preferred embodiment, the temporal response of each sensor (such as resistance as a function of time) is recorded. The temporal response of each sensor can be normalized to a maximum percent increase and percent decrease in response that produces a response pattern associated with the exposure of the analyte. By iterative profiling of known analyses, a structure-function database correlating analyses and response profiles is generated. Unknown analytes, which are optionally chiral analytes, can then be characterized or identified using response pattern comparison and recognition

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algorithms. Accordingly, analyte detection systems comprising sensor arrays, an electrical measuring device for detecting electrical responses across each chemiresistor, a computer, a data structure of sensor array response profiles, and a comparison algorithm are provided. In another embodiment, the electrical measuring device is an integrated

5   circuit comprising neural network-based hardware and a digital-analog converter (DAC) multiplexed to each sensor, or a plurality of DACs, each connected to different sensor(s).

A neural network is a useful tool for analyzing data from unknown analytes and then comparing the data to a known library for quick identification. The neural network is trained using known analytes. Once trained, the neural network then

10   produces an output with the identity of the unknown analyte.

A wide variety of commercial applications are available for the sensors arrays and electronic noses including, but not limited to, environmental toxicology and remediation, biomedicine, materials quality control, food and agricultural products monitoring, heavy industrial manufacturing, ambient air monitoring, worker protection,

15   emissions control, product quality testing, oil/gas petrochemical applications, combustible gas detection, H_2S monitoring, hazardous leak detection and identification, emergency response and law enforcement applications, illegal substance detection and identification, arson investigation, hazardous spill identification, enclosed space surveying, explosives detection, utility and power applications, emissions monitoring, transformer fault

20   detection, food/beverage/agriculture applications, freshness detection, fruit ripening control, fermentation process monitoring and control applications, flavor composition and identification, product quality and identification, refrigerant and fumigant detection, cosmetic/perfume, fragrance formulation, product quality testing, patent protection applications, personal identification, chemical/plastics/pharmaceutical applications,

25   fugitive emission identification, leak detection, solvent recovery effectiveness, perimeter monitoring, product quality testing, hazardous waste site applications, fugitive emission detection and identification, leak detection and identification, perimeter monitoring, transportation, hazardous spill monitoring, refueling operations, shipping container inspection, diesel/gasoline/aviation fuel identification, building/residential natural gas

30   detection, formaldehyde detection, smoke detection, automatic ventilation control applications (cooking, smoking, *etc.*), air intake monitoring, hospital/medical anesthesia & sterilization gas detection, infectious disease detection and breath applications, body fluids analysis, pharmaceutical applications, drug discovery and telesurgery.

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In one embodiment, the sensor arrays of the present invention are used to evaluate the progress of chemical reactions, such as asymmetrical synthesis, in a quantitative or qualitative fashion. In this aspect, the arrays provide quick assays for the enantiomeric excess or purity of compound, such as in a combinatorial library of catalysts

5 forming the compounds of interest. The methods and devices described herein would allow detection and selection of promising leads in a rapid fashion from multiwell plates, and also allow for evaluation of certain compounds for chiral similarity and enantiomeric purity.

The general method for using the disclosed sensors, arrays and electronic

10 noses for detecting the presence of an analyte in a fluid involves resistively sensing the presence of an analyte in a fluid with a chemical sensor comprising first and second conductive leads electrically coupled to and separated by a chemically sensitive resistor as described above by measuring a first resistance between the conductive leads when the resistor is contacted with a first fluid comprising an analyte at a first concentration and a

15 second different resistance when the resistor is contacted with a second fluid comprising the analyte at a second different concentration.

In another embodiment, the present invention relates to a method of detecting and/or discriminating between different chiral compounds, the method comprising exposing a sensor comprising a chiral region to an analyte containing an

20 optically active substance and measuring the response by a detector.

In a preferred embodiment, the sensor arrays of the present invention detect differences in optically active isomers. In theory, the magnitude of the differentiation between enantiomers can be quantified by considering the relative difference in response, Q_{rel}, between the enantiomers:

25                              $$Q_{rel} = [\, \Delta Q_{(+/-)}/Q_{(-)} \,]$$ (1)

where $\Delta Q_{(+/-)}$ is the difference in percent response of a detector when exposed to the (+) and (-) enantiomers of an analyte, respectively. Arbitrarily, as used herein, the value for $\Delta Q(+/-)$ is defined as a positive number.

Using gas chromatography as an analogy, the partition coefficient, K, is

30 defined as $K = C_s/C_v$, where C_s is the concentration of solute in the sorbent phase and C_v is the concentration in the vapor phase at equilibrium. In the experimental protocol defined hereinbelow, C_v is constant since the vapor generation apparatus is continuously

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replenishing the vapor stream. Therefore, a ratio, "a", is defined as the partition coefficients between the two enantiomers, as follows:

$$a = K_1/K_2 = [C_s/C_v]_1/[C_s/C_v]_2 = [C_s]_1/[C_s]_2 \qquad (2)$$

5 To remain consistent with the gas chromatography literature, K_1 is defined as the larger partition coefficient, ensuring that "a" is greater than one. (see, Schurig, V.J. *Chromatogr.* A **1994**, 666, 111.). This corresponds to the analyte which gave the largest response, which, in the examples set forth below, is the (+) enantiomer.

Without being bound by any particular theory, it is believed that the differences in steady-state response for each of the enantiomeric pairs can be attributed to 10 the differences in the free energy, ΔG, of sorption for each enantiomer into the chiral composite (*i.e.*, $\Delta G_1 - \Delta G_2$), or $\Delta_{1,2}(\Delta G)$). The difference in ΔG of sorption is related to the ratio of the partition coefficients as expressed below:

$$\Delta_{1,2}(\Delta G) = -RT \ln(a) \qquad (3)$$

The composite chemiresistor detectors respond linearly to analyte 15 concentrations over at least a factor of 10^2 in concentration, therefore C_s is proportional to Q for such systems. (see, Lonergan, M.C. *et al.*, *Chem. Mater.* **1996**, 8, 2298; Severin, E.J. *et al.*, to be submitted.) Since the vapor concentrations of each enantiomer of an analyte is identical, with only the amount sorbing into the polymer matrix being different, "a" can be related to $Q_{(+)}$ and $Q_{(-)}$ as follows:

20 $$a = [C_s]_1/[C_s]_2 = Q_{(+)}/Q_{(-)} \qquad (4)$$

As described in detail hereinbelow, the values of $\Delta_{1,2}(\Delta G)$ calculated using the percent response data and the relationships of equations 1-4 are set forth in the Example section. These values are similar to the minimum values (ca. -0.1 kJ mol^{-1}) observed for enantiomers in chiral gas chromatography (see, Schurig, V.J. *Chromatogr.* A 25 **1994**, 666, 111).

EXAMPLE

A.   MATERIALS

In this example, carbon black is the conductive region material. The 30 carbon black (Black Pearls 2000) is a furnace black material donated by Cabot Co. (Billerica, MA). The nonconductive region comprised a chiral polymer, namely, poly(R-3-hydroxybutyrate-*co*-R-3-hydroxyvalerate) (77% butyrate), and was obtained from the Goodfellow Corp.(Berwyn, PA). The achiral polymer used for control

experiments was poly(ethylene-co-vinyl acetate) (82% ethylene) (Polysciences Inc.,
Warrington, PA). In this example, the enantiomeric pairs examined were: (+)-2-butanol
and (-)-2-butanol (Aldrich, Milwaukee, WI); (+)-a-pinene and (-)-a-pinene (Fluka,
Ronkonkoma, NY); (+)-epichlorohydrin and (-)-epichlorohydrin (Aldrich), and methyl-
5   (+)-2-chloropropionate and methyl-(-)-2-chloropropionate (Aldrich, Milwaukee, WI).

              An apparatus that provided known partial pressures of the vapors was
constructed using general laboratory glassware. This consisted of a bubbler made from
small 12 mL centrifuge tubes with conical bottoms that were filled to a depth of 3 cm (ca.
2 mL). Into the 1.5 cm diameter mouth of the tube was affixed a two-hole rubber stopper.
10   In each hole was a 5 mm outer diameter glass tube, one of which extended to the bottom
of the bubbler and served as the gas inlet, the other of which extended past the stopper by
only a few mm and served as the gas exit. The carrier gas was nitrogen, obtained from a
commercial gas supply tank. The measurements were performed at room temperature
(23 ± 1 °C).

15   The carrier gas was introduced through the glass tube that extended to the
bottom of the bubbler apparatus, and was bubbled through the solvent, thus saturating it
with the solvent vapor. The saturated vapor was carried out of the bubbler, diluted by
blending with a controlled background flow of pure carrier gas, and then introduced into a
sensing chamber. This chamber consisted of a glass tube (22 cm long with a 2.6 cm inner
20   diameter) to which inlet and outlet sidearms had been attached. The detectors were
introduced into the chamber through a 24/40 standard taper ground glass opening attached
at one end of the chamber. The chamber was then sealed with a ground-glass stopper
through which electrical lead wires for the detectors had been sealed. The gas flow rates
were controlled using needle valves and stopcocks.

25   To prepare the detector substrates, two parallel bands of gold, 50-100 nm
thick and separated by 5 mm, were deposited onto conventional 7.5 cm x 2.5 cm glass
slides. The slides were then cut into strips to produce 0.7 cm x 2.5 cm pieces of glass,
with each strip of glass having one pair of Au leads spaced 5 mm apart.

              The detectors were made from a solution of the polymer into which carbon
30   black had been suspended. In this example, 125 mg of the polymer was dissolved in 10
mL of tetrahydrofuran, and carbon black (42 mg) was then suspended in this solution, to
produce a composition of 75% polymer and 25% carbon black by weight of solids. A

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single solution that contained the polymer and the carbon black was used to prepare all

the detectors of a given composition that were used in this example. Detectors used to

analyze pinene vapors were fabricated slightly differently, having films made from a

suspension with a carbon black loading of 30% by weight of solids. In both cases, an

5   aliquot of the suspension was spin coated, at 1000 rpm, onto a glass substrate using a

Headway (Garland, TX) spin coater, and the resulting film was allowed to dry in air. One

coating of the suspension was applied to each substrate yielding a film thickness of ≈1

micron as determined by atomic force microscopy, except for pinene detectors, for which

six coats of suspension were applied, producing films ≈6 micron in thickness. The

10   detectors with extra coatings gave higher signal-to-noise when used for pinene.

       B.   METHODS

               The dc resistance of each detector was determined as a function of time

       using a simple two-point resistance configuration. Contacts were made to the gold lines

15   by pressure-contacting electrical leads using flat-jawed alligator clips. Resistance data

       were acquired using a Hydra 2620A Data Acquisition Unit (John Fluke Mfg. Co.; Everett,

       WA) which was interfaced to a personal computer. All of the films had resistance values

       below the 10 MΩ limit of the Hydra 2620A.

               To initiate an experiment, five copies of a given detector type were placed

20   into the glass chamber and a background flow of nitrogen was introduced until the

       resistance of the detectors stabilized. Solvent vapor streams were then passed over the

       detectors. The background and analyte flow rates were monitored using two flow meters

       (Gilmont Instruments, Inc.) which had limits of 0.2 L min^{-1} to 15.0 L min^{-1} and 0.0015 L

       min^{-1} to 0.310 L min^{-1}, respectively. In a typical experiment, resistance data on the

25   detectors were collected for 150 s with just the background gas flowing (typically about 1

       - 2 L min^{-1}) to serve as a baseline. This was followed by a 150 s data collection while the

       detectors were exposed to the analyte vapor stream (typically about 200 - 300 mL min^{-1}).

       The detectors were then given 200 - 300 s to recover during which pure background gas

       was passed through the chamber. The exposure times varied, but steady state values of

30   resistance change were always reached for any given exposure time. Resistances for all

       detectors in a given trial were monitored contemporaneously through the use of the

       multiplexing capabilities of the Hydra voltmeter. Results were obtained by running two

trials (except for epichlorohydrin for which three trials were run) of five exposures each, with the trials performed on different days. Each analyte was exposed to five copies of the detector simultaneously and the results were averaged to obtain the reported data set. In the case of epichlrohydrin, a third trial was run using 300 s exposure and recovery

5   times to investigate whether longer time cycles produced different response signals, but the data were essentially identical to those obtained using the shorter detector cycle times described above. The exposures were made at the following concentrations: epichlorohydrin, 3 parts per thousand (ppth); a-pinene, 1 ppth; methyl-2-chloropropionate, 2 ppth; and 2-butanol, 4 ppth. Concentrations were

10   calculated by diluting saturated gas streams to known volumes, and the analyte concentrations were determined from measurements of the flow rate of the gas and the rate of mass loss of the solvent. (*see*, Lonergan, M.C. *et al., Chem. Mater.* **1996**, 8, 2298.)

            The achiral control detectors were made from benzene solutions of

15   poly(ethylene-*co*-vinyl acetate) (82% ethylene) into which carbon black had been suspended. The same type of carbon black was used as for the chiral detector fabrication. Glass slides, containing gold contacts, were coated by dipping the slide into the suspension. Three coatings were applied to each slide. The polymer concentration was 10 mg mL^{-1} and the carbon black loading was 30% by weight of solids. Results were

·20   obtained by running one trial of four (for epichlorohydrin and methyl-2-chloropropionate) or five (for 2-butanol and a-pinene) exposures. Each analyte was exposed to five detectors simultaneously and the results were averaged to obtain the reported data set. The control exposures were made at the following concentrations: epichlorohydrin, 4 ppth; a-pinene, 1 ppth; methyl-2-chloropropionate, 3 ppth; and 2-butanol, 4 ppth.

25   With reference to Figure 1, a typical response of a chiral detector to 2-butanol is illustrated. All the detectors displayed an increase in resistance upon exposure to the vapor, and returned to their baseline values after the vapor was removed. The change in resistance was quite rapid, taking less than 20 s to reach 75% of the final resistance value (taken after 150 s). The responses were analyzed by calculating the

30   maximum differential response value, DR_{max}, observed during the exposure period and dividing it by the baseline value of the resistance, R_b, (taken as the resistance value just before the exposure began) and expressed as a percent change in resistance, Q:

$$Q = (DR_{max}/R_b)*100 \qquad\qquad (5)$$

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$Q_{(+)}$ and $Q_{(-)}$ correspond to the percent relative differential resistance response for the (+) and (-) enantiomers respectively. A representative data set, for the enantiomers of 2-butanol and the control, is presented in Tables 2-3, while Table 5 summarizes the data.

As shown in Tables 2-5, statistically significant differences in detector response were observed when enantiomers of a given analyte were exposed to the chiral carbon black-polymer composite detectors. In contrast, no statistically significant difference in response was observed when achiral detectors were exposed to these same enantiomers.

Table 2. Data[b] from trial 1 for the (+) and (-) Enantiomers of 2-Butanol.

Trial 1 Detector #	$Q_{(-)}$[a]	$Q_{(+)}$[a]	$\Delta Q_{(+/-)}$	Q_{rel}	α	$\Delta_{1,2}(\Delta G)$ kJ/mol
1	3.41(0.01)	3.60(0.03)	0.19	5.5%	1.06	-0.133
2	3.29(0.02)	3.52(0.03)	0.23	7.0%	1.07	-0.167
3	2.89(0.02)	3.10(0.02)	0.21	7.3%	1.07	-0.174
4	2.96(0.02)	3.17(0.03)	0.21	7.0%	1.07	-0.166
5	2.75(0.03)	2.97(0.04)	0.22	8.0%	1.08	-0.189
Average			0.21(0.02)	7.0(0.9)%	1.07(0.01)	-0.17(0.02)

Table 3. Data[b] from trial 2 for the (+) and (-) Enantiomers of 2-Butanol.

Trial 2 Detector #	$Q_{(-)}$[a]	$Q_{(+)}$[a]	$\Delta Q_{(+/-)}$	Q_{rel}	α	$\Delta_{1,2}(\Delta G)$ kJ/mol
1	2.71(0.04)	2.97(0.04)	0.26	9.5%	1.10	-0.224
2	2.59(0.02)	2.87(0.04)	0.28	11%	1.11	-0.253
3	2.55(0.03)	2.79(0.04)	0.24	9.5%	1.10	-0.224
4	2.62(0.03)	2.86(0.04)	0.24	9.2%	1.09	-0.216
5	2.49(0.03)	2.73(0.04)	0.24	9.6%	1.10	-0.225
Average			0.25(0.02)	9.7(0.6)%	1.10(0.01)	-0.23(0.01)

[a] Q(+) and Q(-) correspond to the percent relative differential resistance change averaged over five exposures for the (+) and (-) enantiomers, respectively. α is defined as K_1/K_2, where K1 is defined as the larger partition coefficient.

[b] The numbers in parentheses are estimated standard deviations.

Table 4. Control Data[b] from trial 2 for the (+) and (-) Enantiomers of 2-Butanol.

Control Detector #	$Q_{(-)}$[a]	$Q_{(+)}$[a]	$\Delta Q_{(+/-)}$
1	2.71(0.02)	2.73(0.06)	0.02
2	2.50(0.01)	2.50(0.01)	0.00
3	2.58(0.03)	2.56(0.02)	-0.02
4	3.02(0.03)	3.04(0.01)	0.02
Average			0.00(0.02)

[a] $Q(+)$ and $Q(-)$ correspond to the percent relative differential resistance change averaged over five exposures for the (+) and (-) enantiomers, respectively. α is defined as K_1/K_2, where K1 is defined as the larger partition coefficient.

[b] The numbers in parentheses are estimated standard deviations.

Table 5. Differences in Percent Response[a], $\Delta Q_{(+/-)}$, Observed for Chiral Detectors During Exposure to the (+) and (-) Enantiomers of Four Test Vapors.

Analyte	Trial	$\Delta Q_{(+/-)}$	Q_{rel}	Avg α	Avg $\Delta_{1,2}(\Delta G)$ kJ/mol
2-Butanol	Trial 1	0.21(0.02)	7.0(0.9)%	1.07(0.01)	-0.17(0.02)
	Trial 2	0.25(0.02)	9.8(0.6)%	1.10(0.01)	-0.23(0.01)
	control	0.02(0.01)			
α-Pinene	Trial 1	0.15(0.01)	7.6(1.5)%	1.08(0.01)	-0.18(0.03)
	Trial 2	0.15(0.04)	8.0(1.1)%	1.08(0.01)	-0.19(0.02)
	control	0.02(0.01)			
Epichlorohydrin	Trial 1	0.22(0.01)	6.9(0.6)%	1.07(0.01)	-0.16(0.02)
	Trial 2	0.19(0.03)	5.6(0.6)%	1.06(0.01)	-0.13(0.01)
	Trial 3	0.24(0.03)	7.1(1.2)%	1.07(0.01)	-0.17(0.03)
	control	0.03(0.03)			
Methyl-2-chloropropionate	Trial 1	0.26(0.03)	9.1(1.2)%	1.09(0.01)	-0.21(0.03)
	Trial 2	0.26(0.01)	8.9(0.6)%	1.09(0.01)	-0.21(0.01)
	control	0.02(0.01)			

5   [a] The values tabulated are the percent response values that were averaged over five nominally identical detectors, each of which had been exposed four (for epichlorohydrin and methyl-2-chloropropionate) or five (for 2-butanol and α-pinene) times to the analyte vapor. The other quantities were calculated using the formulas and definitions given in the text.

All publications, patents and patent applications mentioned in this specification are herein incorporated by reference into the specification in their entirety for all purposes. Although the invention has been described with reference to preferred

5 embodiments and examples thereof, the scope of the present invention is not limited only to those described embodiments. As will be apparent to persons skilled in the art, modifications and adaptations to the above-described invention can be made without departing from the spirit and scope of the invention, which is defined and circumscribed by the appended claims.

10

WHAT IS CLAIMED IS

1   **1.**   A device for detecting the presence or absence of an analyte in a
2   fluid, said device comprising a sensor, said sensor comprising a chiral region.

1   **2.**   A device in accordance with claim 1, wherein said sensor
2   comprises a conductive region, a nonconductive region, or mixtures thereof.

1   **3.**   A device in accordance with claim 1, wherein said sensor
2   comprises a conductive region and a nonconductive region, wherein at least one of said
3   conducting and nonconducting regions is a chiral region and wherein said analyte
4   generates a differential response across said sensor.

1   **4.**   A device in accordance with claim 3, wherein said sensor
2   comprises an array of sensors, wherein one of said array of sensors comprises a
3   conductive region and a nonconductive region, and wherein at least one of said
4   conducting and nonconducting regions is a chiral region.

1   **5.**   A device in accordance with claim 3, wherein said conductive
2   region is a conductive material and said nonconductive region is an organic material.

1   **6.**   A device in accordance with claim 3, wherein said conductive
2   region and said nonconductive region alternate.

1   **7.**   A device in accordance with claim 3, wherein said chiral region is
2   a member selected from the group consisting of said conductive region, said
3   nonconductive region and both of said conductive and said nonconductive regions.

1   **8.**   A device in accordance with claim 4, wherein said chiral region
2   comprises a chiral resolving agent.

1   **9.**   A device in accordance with claim 8, wherein said chiral region
2   comprises a chiral polymer.

1   10.   A device in accordance with claim 9, wherein said chiral polymer
2   is a co-polymer.

1   11.   A device in accordance with claim 9, wherein said chiral polymer
2   is cross-linked.

1   12.   A device in accordance with claim 9, wherein said chiral polymer
2   is different in at least two of the sensors.

1   13.   A device in accordance with claim 9, wherein the concentration of
2   said chiral polymer is different in at least two of the sensors.

1   14.   A device in accordance with claim 3, wherein said nonconductive
2   region comprises an organic polymer.

1   15.   A device in accordance with claim 14, wherein said organic
2   polymer is chiral.

1   16.   A device in accordance with claim 15, wherein said chiral co-
2   polymer is poly(R-3-hydroxybutyrate-co-R-3-hydroxyvalerate).

1   17.   A device in accordance with claim 3, wherein said conductive
2   region comprises a member selected from the group consisting of an organic conductor,
3   an inorganic conductor and a mixed inorganic/organic conductor.

1   18.   A device in accordance with claim 17, wherein said conductive
2   region is an inorganic conductor.

1   19.   A device in accordance with claim 17, wherein said conductive
2   region is an organic conductor.

1   20.   A device in accordance with claim 17, wherein said conductive
2   region is chiral.

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1   21.   A device in accordance with claim 19, wherein said organic

2   conductor is carbon black.

1   22.   A device in accordance with claim 3, wherein said conductive

2   region is a particulate material and said chiral nonconductive region is an organic matrix

3   that separates the particulate material thereby providing gaps in the electrical path.

1   23.   A device in accordance with claim 2, wherein at least two sensors

2   are compositionally different.

1   24.   A device in accordance with claim 4, wherein said array of sensors

2   comprise about 10 to about 100 sensors.

1   25.   A device in accordance with claim 4, wherein said array of sensors

2   comprise about 100 to about 1000 sensors.

1   26.   A device in accordance with claim 4, wherein said array of sensors

2   comprise about 1000 to about 10^6 sensors.

1   27.   A device in accordance with claim 4, wherein said sensor array is

2   fabricated using a technique selected from the group consisting of solution casting routes,

3   suspension casting or mechanical mixing.

1   28.   A device in accordance with claim 4, wherein said sensor array is

2   deposited on a chemically inert substrate.

1   29.   A device in accordance with claim 4, wherein said sensor array is

2   fabricated using integrated circuit design.

1   30.   A device in accordance with claim 4, wherein each sensor of said

2   array comprises an electrical lead optionally interdigitized to maximize signal-to-noise

3   ratio.

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1   31.   A device in accordance with claim 4, wherein said sensor array is
2   fabricated onto a micro-chip optionally using ink-jet technology.

1   32.   A device in accordance with claim 3, wherein said differential
2   response is an electrical resistance.

1   33.   A device in accordance with claim 27, wherein said sensor array is
2   fabricated using a solution casting route and said solution cast route is a member selected
3   from the group consisting of spin, spray or dip coating.

1   34.   A device in accordance with claim 4, further comprising a neural
2   network for software or hardware analysis.

1   35.   A device in accordance with claim 3, wherein said analyte is a
2   member selected from the group consisting of alkanes, alkenes, alkynes, dienes, alicyclic
3   hydrocarbons, arenes, alcohols, ethers, ketones, aldehydes, carbonyls, carbanions,
4   polynuclear aromatics, organic derivatives, biomolecules, microorganisms, sugars,
5   isoprenes and isoprenoids, fatty acids and their derivatives.

1   36.   A device in accordance with claim 1, wherein said sensor is a
2   member of the group consisting of thermal sensors, radiation sensors, mechanical sensors,
3   magnetic sensors, chemical sensors, biological sensors and electrical sensors.

1   37.   A device in accordance with claim 36, wherein said sensor is a
2   member of the group consisting of metal oxide sensors, Tuguchi gas sensors, catalytic gas
3   sensors, organic semiconducting gas sensors, solid electrolyte gas sensors, piezoelectric
4   quartz crystal sensors, fiber optic probes and Langmuir-Blodgett films.

1   38.   A device in accordance with claim 3, wherein said detection is
2   carried out in an application selected from the group consisting of environmental
3   toxicology, remediation, biomedicine, material quality control, food monitoring and
4   agricultural monitoring.

1   39.   A method for detecting an analyte in a fluid, said method
2   comprising:

3   contacting a device with said analyte, said device comprising a sensor, said

4   sensor comprising a chiral region; and

5   measuring a response from a detector connected to said sensor, thereby

6   detecting said analyte.

1   40.   A method in accordance with claim 39, wherein said sensor

2   comprises a conductive region, a nonconductive region, or mixtures thereof.

1   41.   A method in accordance with claim 39, wherein said sensor

2   comprises a conductive region and a nonconductive region, wherein at least one of said

3   conducting and nonconducting regions is a chiral region and wherein said analyte

4   generates a differential response across said sensor; and

5   measuring said response from a detector connected to said sensor, thereby

6   detecting said analyte.

1   42.   A method in accordance with claim 41, wherein said sensor is an

2   array of sensors, wherein one of said array of sensors comprises a conductive region and a

3   nonconductive region, wherein at least one of said conducting and nonconducting regions

4   is a chiral region.

1   43.   A method in accordance with claim 41, wherein said conductive

2   region is a conductive material and said nonconductive region is an organic material.

1   44.   A method in accordance with claim 41, wherein said conductive

2   region and said nonconductive region alternate.

1   45.   A method in accordance with claim 41, wherein said chiral region

2   comprises a chiral polymer.

1   46.   A method in accordance with claim 45, wherein said chiral

2   polymer is a co-polymer.

1   47.   A method in accordance with claim 41, wherein said

2   nonconductive region is a chiral polymer.

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1   48.   A method in accordance with claim 47, wherein said polymer is

2   poly(R-3-hydroxybutyrate-co-R-3-hydroxyvalerate).

1   49.   A method in accordance with claim 42, wherein each sensor of said

2   array comprises an electrical lead optionally interdigitized to maximize signal-to-noise

3   ratio.

1   50.   A method in accordance with claim 41, wherein said analyte is a

2   member selected from the group consisting of alkanes, alkenes, alkynes, dienes, alicyclic

3   hydrocarbons, arenes, alcohols, ethers, ketones, aldehydes, carbonyls, carbanions,

4   polynuclear aromatics, organic derivatives, biomolecules, microorganisms, sugars,

5   isoprenes and isoprenoids, fatty acids and their derivatives.

1   51.   A method in accordance with claim 41, wherein said detection is

2   carried out in an application selected from the group consisting of environmental

3   toxicology, remediation, biomedicine, material quality control, food monitoring and

4   agricultural monitoring.

1   52.   A method in accordance with claim 42, wherein said array of

2   sensors comprise about 10 to about 100 sensors.

1   53.   A method in accordance with claim 42, wherein said array of

2   sensors comprise about 100 to about 1000 sensors.

1   54.   A method in accordance with claim 42, wherein said array of

2   sensors comprises about 1000 to about 10^6 sensors.

1   55.   A method in accordance with claim 41, wherein said conductive

2   region comprises a member selected from the group consisting of an organic conductor,

3   an inorganic conductor and a mixed inorganic/organic conductor.

1   56.   A method in accordance with claim 42, wherein at least two of said

2   sensors are compositionally different.

1   57.   A method in accordance with claim 39, wherein said sensor is a
2   member of the group consisting of thermal sensors, radiation sensors, mechanical
3   sensors, magnetic sensors, chemical sensors, biological sensors and electrical sensors.

1   58.   A method in accordance with claim 57, wherein said sensor is a
2   member of the group consisting of metal oxide sensors, Tuguchi gas sensors, catalytic gas
3   sensors, organic semiconducting gas sensors, solid electrolyte gas sensors, piezoelectric
4   quartz crystal sensors, fiber optic probes and Langmuir-Blodgett films.

1   59.   A device for detecting the presence or absence of an analyte in a
2   fluid, said device producing one signal in the presence of one form on a chiral analyte and
3   a second, diffferent signal in the presence of the other form of said chiral analyte.

1   60.   A device in accordance with claim 1, wherein said sensor provides
2   an electrical signal as its output.

1   61.   A device in accordance with claim 1, wherein said sensor provides
2   an electrical signal as its output, said output is a member of the group consisting of
3   resistance, impedance, conductance capacitance and inductance.

FIGURE 1
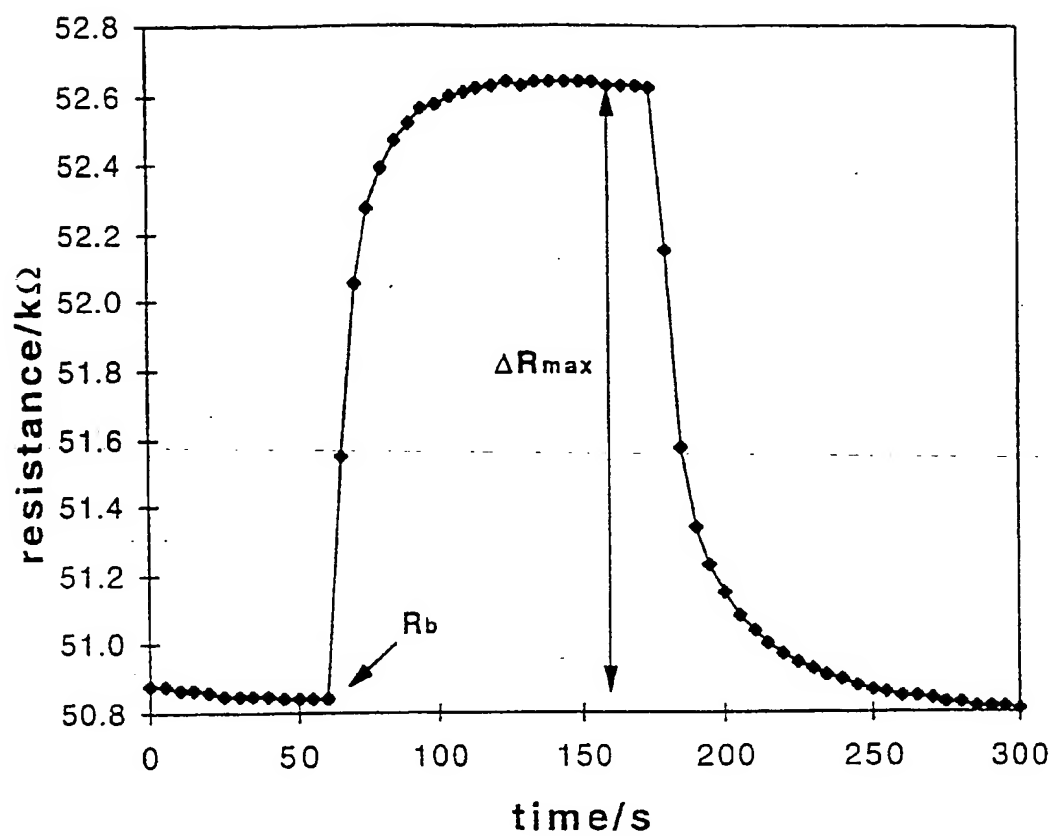
INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/02461

A.	CLASSIFICATION OF SUBJECT MATTER

IPC(6)   :G01N 31/00, 33/00
US CL   :422/68.1, 82.01, 82.02

According to International Patent Classification (IPC) or to both national classification and IPC

B.	FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

   U.S. :   422/68.1, 82.01, 82.02; 73/23.34

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

   None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

   Please See Extra Sheet.

C.	DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	EP 000794428 A1 (COOKE et al) 10 September 1997 (10.09.97) abstract, column 1, lines 48-50, 57-58, column 2, lines 1-20, column 6, lines 9-10.	1-2, 36-37, 60-61 ---------------- 3-14, 17-18, 23-26, 32, 35, 38
Y	US 5,571,401 A (LEWIS et al.) 05 November 1996 (05.11.96) abstract, column 2, lines 27-33, column 7, lines 18-23.	23-26
A	JP 09176243 A (OKAMOTO et al.) 08 July 1997 (08.07.97) SEE ABSTRACT ATTACHED	
A	US 5,122,472 A (SILKS, III et al.) 16 June 1992 (16.06.92)	

X	Further documents are listed in the continuation of Box C.		See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search 20 APRIL 1999	Date of mailing of the international search report **13 MAY 1999**
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Kevin P. Cannell Telephone No. (703) 305-0661

Form PCT/ISA/210 (second sheet)(July 1992)*

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,674,752 A (BUCKLEY et al.) 07 October 1997 (07.10.97)	

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS - search terms: chiral(5a)(sensor or region or component or part), electronic nose, enantiomer, sensor(2a)array, conducti? and nonconducti?
STN/CAS - search terms: (sensing or detecting or sensor or detector or detection)(6a)(chiral or enantiomer)

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-38 and 60-61, drawn to a device for detecting an analyte.
Group II, claim(s) 39-58, drawn to a method for detecting an analyte.
Group III, claim 59, drawn to a method for detecting an analyte.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The inventions of groups I and II share a special technical feature in that the sensor comprises a chiral region. However, this special technical feature does not define a contribution over the prior art. The teachings of Cooke et al. anticipate a sensor for detecting the presence or absence of an analyte using a sensor comprising a chiral region. Cooke et al. teach a semi-conductive polymer material wherein the polymer material contains chiral sites. The abstract and column 2, lines 39-58, column 3, and column 4, lines 1-20 disclose the sensor taught by Cooke et al.

The inventions listed as Groups I and III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The inventions of groups I and III lack a common special technical feature. The device of group I requires the sensor to comprise a chiral region. The device of group III does not require the sensor to comprise a chiral region.

The inventions listed as Groups II and III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The inventions of groups II and III lack a common special technical feature. The method of detecting an analyte in group II requires a sensor with a chiral region. The device of group III, however, does not require a chiral region for detecting analytes.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/02461

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

   Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
   1-38 and 60-61

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.

   ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)*